ORİJİNAL ARAŞTIRMA ORIGINAL RESEARCH

Time-Dependent Area Under the ROC Curve for Optimum Biological Dose Detection

Optimum Biyolojik Doz Tespiti için ROC Eğrisi Altında Zamana Bağlı Alan

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ABSTRACT Objective: In Metronomic Chemotherapy (MC) performance of specific surrogate markers plays an important role to obtain the effective treatment. It is very difficult to detect the initial threshold value of surrogate markers to get an idea about optimum dose level of MC for long-term effective treatment. The long-term effective treatment can be obtained through controlling the surrogate markers on continues measured value into a specific range. The long-term effective treatment is defined as long-term recurrence-free survival. During the treatment initiation, many surrogate markers value changes rapidly and those values are time-dependent measurements. The specification of surrogate markers threshold value can only be obtained through the application of ROC curve (AUC), Sensitivity, and Specificity analysis. **Material and Methods:** The application of ROC curve to detect the time-dependent continuous measurement becomes complicated. In this paper, a straightforward Survival Analysis estimator through MCMC iteration for each possible time point measurement is adopted to detect the possible threshold value of surrogate markers. **Results:** The surrogate markers levels on angiogenesis in Head and Neck Cancer (HNC) patients are considered. **Conclusion**: The threshold value of the surrogate markers is detected through the formation of ROC curve.

Key Words: ROC curves; area under the curve; sensitivity; specificity; risk prediction; Kaplan-Meier estimator

ÖZET Amaç: Metronomik kemoterapide (MK) belirli taşıyıcı markırların performansı etkili tedaviyi elde etmede önemli rol oynamaktadır. Uzun dönem etkili tedavi için MK'nın optimum doz düzeyi hakkında fikir edinmek için taşıyıcı markırların ilk eşik değerini tespit etmek zordur. Uzun dönem etkili tedavi, taşıyıcı markırların belirli bir değişim aralığında sürekli ölçülmüş değerini kontrol ederek elde edilebilir. Uzun dönem etkili tedavi, uzun dönem nükssüz sağkalım olarak tanımlanır. Tedavi başlangıcı boyunca, birçok taşıyıcı markır değeri hızla değişir ve bu değerler zamana bağlı ölçümlerdir. Taşıyıcı markırların eşik değerlerinin belirlenmesi yalnızca ROC eğrisi (AUC), duyarlılık tanımlayıcılık analiz uygulamalarıyla elde edilebilir. **Gereç ve Yöntemler:** Zamana bağlı sürekli ölçümleri tespit etmek için ROC eğrisinin uygulanması karmaşık hale gelir. Bu makalede, taşıyıcı markırların olası eşik değerlerini tespit etmek için her olası zamana bağlı ölçüm için MCMC iterasyonu yoluyla Sağkalım analiz tahmin edicisi kullanılmıştır. **Bulgular:** Baş ve boyun kanseri (BBK) hastalarında anjiyogenezde taşıyıcı markır düzeyleri dikkate alınmıştır. **Sonuç:** Taşıyıcı markırların eşik değeri ROC eğrisinin oluşumuyla tespit edilmiştir.

Anahtar Kelimeler: ROC eğrileri; eğri altında kalan alan; duyarlılık; tanımlayıcılık; risk tahmini; Kaplan-Meier tahmincisi

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The ROC curves are accepted as having several attractive options in diagnostic medicine. The ROC provides the natural inequity capacity of a test without considering it to any specific threshold. The ROC curves are particularly important for comparing the inequity of different diagnostic markers. It can be adopted as a valid procedure when biomarkers are on completely measured in different occasions. The ROC is free from disease prevalence and hence can be estimated from the experimental study itself.[1] The doses of chemotherapy selected in clinical practice are routinely derived from the maximum tolerable dose(MTD) approaches. It is believed that an increase in dose will lead to an increase in tumor response. The dose selected for phase 2 and further studies is one dose level below the MTD level in Phase I studies.[2-4] However, this conventional dosing of chemotherapy has routinely compromised the QOL of patients and may lead to a selection of chemo-resistant clones.[5-7]

Chemo-resistance and toxic effects are the major problems in chemotherapy drug administration. A new modality of drug administration has emerged is known as "metronomic chemotherapy (MC)". It has been suggested as an alternative strategy to overcome such effects. It provides repeated administration of conventional chemotherapeutic agents at very low doses. It gives a rare chance of developing acquired drug resistance.[8] Studies of tumor endothelial cells through pharmacogenomic and pharmacoproteomic effects are required to be performed to explore the information about an effective surrogate marker(SM) to provide the best treatment combinations for each tumor type and patient population.[9]

A key scientific question is whether the SM's specific level measured during MC initiations can contribute towards long-term effective treatment. The precision through the sensitivity and specificity of SM's continuous measurement are required to be established for specific MC dose level on site wise tumor growth. The aim of this manuscript is to extend the concepts of sensitivity and specificity of time-dependent continuous measurement, allowing classification of diagnostic accuracy for MC treatment outcomes.

MATERIAL AND METHODS

The survival function is defined with

$$S(t_{(j)}) = \frac{R(t_{(j)}) - d_i}{n} \text{ for j} = 1,2,\dots \text{n} \quad (1)$$

The term n is the total sample size and $R(t_{(i)})$ is the individual at risk at time point t_j.

It is assumed with

$$S(t_{(j)}) = S(t_{(j-1)})P[T > t_{(j)} | T \geq t_{(j)}] \text{for j} = 1,2,\dots \text{m} \quad (2)$$

The number of order times (recurrence and censored) is defined with m. The process of iteration started with known value from$S(t_{(0)})$.

It is assumed that the number of cancer patients recurred are presented with ordered times follows the binomial distribution

$$d[i] \sim \text{binomial}(q[i], R[i]) \quad (3)$$

The probability of recurrence and individual at risk are defined as q[i] and R[i] respectively.

The q[i] is assumed with

$$q[i] \sim \text{beta}(0.01,0.01) \quad (4)$$

The posterior mean of$S(t_{(i)})$ is utilized to get the recurrence probability.

The conditional probabilities is formed with

$$P[T > t_{(i)} | T \geq t_{(i)}] \text{for i} = 1,2,\dots \text{m} \quad (5)$$

The censored observations is defined as

$$c[i] \sim \text{binomial}(qc[i], R[i]) \quad (6)$$

and

$$\text{q}c[i] \sim \text{beta}(0.01,0.01) \quad (7)$$

The number at risk at time i is R[i] with

$$R[i] = R[i-1] - c[i-1] - d[i-1] \text{ for i} = 2,3,\dots \text{m, where m is the number of distinct ordered times} \quad (8)$$

The dose of MC is separated with levels and defined as group$_1$ and group$_2$.

The expected number of events for group$_1$ and group$_2$ are defined with

$$a_{1i} = \left[\frac{R_1(i)}{R_1(i)+R_2(i)}\right](d_{1i} + d_{2i}) \text{ and}$$
$$a_{2i} = \left[\frac{R_2(i)}{R_1(i)+R_2(i)}\right](d_{1i} + d_{2i}) \text{respectively} \quad (9)$$

The sum of observed minus and expected difference for group$_1$ and group$_2$ is defined as

$$v_1 = \sum_{i=1}^{m}(d_{1i} - a_{1i}) \text{and}$$
$$v_2 = \sum_{i=1}^{m}(d_{2i} - a_{2i}) \text{ respectively} \quad (10)$$

It is assumed that the probability of a recurrence for both the treated group is equal.

The Bayesian likelihood ratio is defined as

$$L = \frac{v_1 \times v_1}{e_1} + \frac{v_2 \times v_2}{e_2}, \text{where } e_1 = \sum_{i=1}^{m} a_{1i} \text{ and } e_2 = \sum_{i=1}^{m} a_{2i} \quad (11)$$

LIKELIHOOD

The cumulative hazard function H(t) is defined as

$$H(t) = -\log\big(S(t)\big) \quad (12)$$

The function S(t) is the survival function.[10,11]

The cumulative hazard function H(t) is defined with

$$H(t) = \int_{[0,t]} \frac{dF(u)}{S(u)} \quad (13)$$

Where

$$F(t) = 1 - S(t) = 1 - \prod_{[0,t]}\{1 - dH(t)\} \quad (14)$$

This cumulative hazard function H(t) is more appropriate for distribution with continuous measurement. The prior distribution in this setting is defined as

$$dH(s) \sim B\left(c(s)dH*(s), c(s)\big(1 - dH*(s)\big)\right) \quad (15)$$

where c(s)dH*(s) and c(s)(1-dH*(s)) represents the scale and shape parameters with beta distribution.

The distribution of H(s) is approximated with beta distribution with finite range. It is promising to work with beta distribution for the baseline cumulative hazard appropriated through a Cox model with time continuous measurement.[12]

However it is more convenient to work with categorized version of the beta distribution.[13,14] The corresponding likelihood is defined below.

Suppose the Cox model is defined as

$$S(s_j|x) = P(T > s_j|x) = \prod_{k=1}^{J}(1 - h_k)^{\exp(x'\beta)} \quad (16)$$

The term h_k is the baseline hazard rate for the interval $I_k=(s_{k-1}, s_k]$.

The likelihood is defined as

$$L(\beta, h) = \prod_{j=1}^{J}((1 - h_j)^{\sum_{l \epsilon R_j - D_j} \exp(x_l'\beta)} \prod_{l \epsilon D_j}(1 - (1 - h_j)^{\exp(x_l'\beta)} \quad (17)$$

where $h=(h_1, h_2,\ldots,h_J)'$.The independent beta priors for the h_k's are assumed with $h \sim \beta\big(c_{0k}\alpha_{0k}, c_{0k}(1 - \alpha_{0k})\big)$ and those are independent for k=1,2, . . . , J.

It is assumed that h_k are independent from other priors. The continuous-time point measurement has been considered to obtain the beta distribution approximated for h_k. It can perform well with separated interval I_k.

The prior density of h is defined with

$$\pi(h) \propto \prod_{j=1}^{J} h_j^{c_{0j}\alpha_{0j}-1}(1 - h_j)^{c_{0j}(1-\alpha_{0j})-1} \quad (18)$$

Further it is assumed with $\beta \sim N(\mu_0, \sigma_0)$ as independent of h.

The joint posterior of (β, h) is defined with

$$\pi(\beta, h|D) \propto \prod_{j=1}^{J}((1 - h_j)^{\sum_{l \epsilon R_j - D_j} \exp(x_l'\beta))} \prod_{l \epsilon D_j}(1 - (1 - h_j)^{\exp(x_l'\beta)} \times$$
$$\prod_{j=1}^{J} h_j^{c_{0j}\alpha_{0j}-1}(1 - h_j)^{c_{0j}(1-\alpha_{0j})-1}\pi(\beta) \quad (19)$$

The hazard h_j is defined with

$$h_j = P[(s_j \geq Y > s_{j-1}|Y > s_{j-1})] \quad (20)$$

Therefore, the survival curve is defined as

$$S(s) = \prod_{k=1}^{j}(1 - h_k) \quad (21)$$

The prior distribution of h_j is obtained with

$$h_j \sim \beta\big(c_{0j}\alpha_{0j}, c_{0j}(1 - \alpha_{0j})\big) \text{for j} = 1,2, \ldots . \text{J} \quad (22)$$

The h_j's are independent with mean α_{0j} and variance $\alpha_{0j}(1 - \alpha_{0j})/(c_{0j} + 1)$.

The term C_{0j} is adopted to measure the confidence interval approximated with prior mean α_{0j} of the hazard rate h_j in I_j.

The posterior distribution of the h_j is obtained with

$$h_j|D \sim \beta\left(c_{0j}\alpha_{0j} + d_j, c_{0j}(1-\alpha_{0j}) + r_j - d_j\right) \quad (23)$$

where $D = \{(d_j, r_j), j = 1,2,\ldots J\}$ denotes the complete grouped data.[15]

ROC, SENSITIVITY AND SPECIFICITY

Receiver operating characteristic (ROC) curves are widely adopted to measure the performance of diagnostic tools and prognostic biomarkers. Suppose the continuous SM measurements after administration of MC are considered to identify Head and Neck(HNC) patients will recur or not. The measurement of SM is performed through the specific diagnostic test. Let Y be the value of the SM measurements. It is assumed with a continuous random variable having distribution F_R in the recurred and F_{NR} in the non-recurred HNC patients. Further, it is assumed that the SM tends to be increased in the recurred patients. The given threshold value c, that is Y>c is considered. However, the lower values of *c* tend to low false-negative rates but high false-positive rates. However, high values of *c* lead to high false-negative rates but low false-positive rates. The ROC curve is used to make tradeoffs between true and false positives on different combination of discrimination on threshold value of *c*.

It can be assumed with $\{(FPR(c), TPR(c)): c_i \epsilon (-\infty, \infty)\}$. The false-positive rate is defined as $FPR(c) = 1 - F_R(c) = \overline{F_R}(c)$ and the true-positive rate is $TPR(c) = 1 - F(c) = \overline{F_{NR}}(c)$

The ROC can be expressed with curve by

$$\eta(u) = \bar{F}_{NR}\left(\bar{F}_R^{-1}\right), 0 \le u \le 1 \quad (24)$$

The method explained above is simple and suitable when all HNC patients are observed for the same length of time. It is to be noted that the MC administration and corresponding measurement of SM are time dependent. It is possible to fit the model through follow-up time measurements. It can be estimated through survival analysis to capture the variation with time. It takes consideration of time-dependent ROC, AUC, sensitivity and specificity. The term *AUC(t)* provides the probability that a person with HNC patients with recurrence by time *t* has a higher value of SM measurements than an HNC patients with no recurrence by time *t*. Let the HNC patients "i" with risk of having recurrence before the time τ is $\{X_i > c_{i\tau}\}$. The threshold value of the SM is defined as $c_{i\tau}$. The sensitivity (se) and the specificity (sp) of the SM is defined as X_i for the prediction of the failure "i", i.e. $P(X_i > c_{i\tau}|T \le \tau)$ and $P(X_i \le c_{i\tau}|T > \tau)$ with

$$se_i(c_{i\tau}|\tau) = \frac{\int_{c_{i\tau}}^{\infty}(1-S_i(\tau|x_i))g_i(x_i)dx_i}{\int_{-\infty}^{\infty}(1-S_i(\tau|x_i))g_i(x_i)dx_i} \quad (25)$$

$$sp_i(c_{i\tau}|\tau) = \frac{\int_{\infty}^{c_{i\tau}}(1-S_i(\tau|x_i))g_i(x_i)dx_i}{\int_{-\infty}^{\infty}(1-S_i(\tau|x_i))g_i(x_i)dx_i} \quad (26)$$

The probability density function $g_i(x_i)$ is used for the continuous SM value with x_i. The sensitivity is defined as the probability of being at risk given that a failure *"i"* occurs before time τ. The specificity is defined as the probability of not being at risk given that a failure *"i"* does not occur before time τ. It is very important to be considered about the selection of τ during the observation duration where the sufficient number of patients will be present to get the predicted results.

APPLICATION ON METRONOMIC CHEMOTHERAPY DATA

The clinical goal is to find the optimum Biological Dose of MC of two dose level i.e. 15mg/m^2 and 10mg/m^2 for predicting the long term non-recurrence rate among HNC patients. The specific idea is to study the level of serum creatinine levels (SCR) and define the threshold value for a

duration of administration of MC on 1,3,5,7,9 and 11th weeks. The maximum days to monitor the level of SM is specified as τ=80 days. A total of 63 patients were separated for MC therapy of dose level 15mg/m^2(termed as group$_1$) and 10 mg/m^2 (termed as group$_2$).A total of 11 patient's SM value were observed with more than threshold value in group$_1$ and a total of 19 patients in group$_2$.However, during the MC therapy, the schedule has been finalized for each patient with individual specific prognostic function. It is assumed that the level of SM will not be more than the threshold value at any point of time. The probabilities of an event for 80 days for individuals are detailed in Table 1. The proposed method has been illustrated on MC therapy. The results are detailed in Table 1 and corresponding data explored in Figure 1.

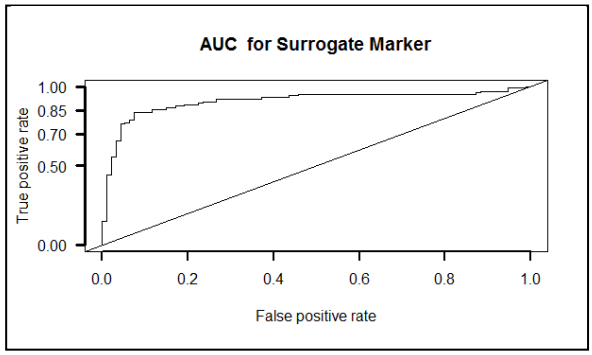

FIGURE 1: AUC for Surrogate Marker.

RESULT AND DISCUSSION

The initial study report on MC presented and the overall survival (OS) was also increased significantly in the MCT arm.[16] In a case of OBD, the widely adopted method is trinomial continual reassessment, where the highest probability of toxic effect is considered.[16] Low-dose chemotherapy drugs are more effective to suppress tumors by restraining tumor vessel growth and preventing the repair of damaged vascular endothelial cells.[17] A high-dose chemotherapy drug like Cisplatin contributes to serious side effects.[18] The target of MC therapy is the vascular endothelial cells.[19] The growth of new vessels for a long-term survival time treated with traditional maximum tolerated dose (MTD) through high-dose chemotherapy has been confirmed.[20] The anti-angiogenic plays the important role as clinical potential.[21] The metastasis and the growth of tumor cells depend on neovascularization.[20] The anti-tumor drugs could cause inhibition of tumor neovascularity.[23] The SCR have emerged as a promising candidate surrogate marker to assess

TABLE 1: Operating characteristics of optimum biological dose.

	True Probability	
	group$_1$	group$_2$
No of Patients	32	31
Within the Threshold limit value	21	12

TABLE 2: True values of AUC and means and standard deviation (SD) obtained from MCMC.

Time Point	Group$_1$			Group$_2$		
In Weeks	AUC	Mean	SD	AUC	Mean	SD
1	0.6116	0.6121	0.0312	0.6132	0.6111	0.00113
3	0.6191	0.6156	0.0432	0.6321	0.6314	0.0111
5	0.6536	0.6532	0.0224	0.6625	0.6616	0.0109
7	0.6212	0.6223	0.0142	0.6147	0.6127	0.0201
9	0.6241	0.6213	0.0325	0.6285	0.6215	0.0117
11	0.6627	0.6619	0.0356	0.6265	0.6245	0.0117

TABLE 3: Posterior estimates observed from MCMC iterations.

Parameter	Mean	SD	2.5%	97.5%
β_1	1.626	0.431	0.817	2.487
β_2	1.286	1.114	-0.746	3.586
$group_{11}$	0.470	0.388	0.000	0.993
$group_{12}$	0.345	0.366	0.000	0.980
$group_{13}$	0.306	0.354	0.000	0.973
$group_{14}$	0.252	0.333	0.000	0.958
$group_{15}$	0.213	0.313	0.000	0.944
$group_{16}$	0.172	0.287	0.000	0.917
$group_{21}$	0.801	0.270	0.005	0.998
$group_{22}$	0.697	0.317	0.000	0.993
$group_{23}$	0.656	0.330	0.000	0.991
$group_{24}$	0.588	0.343	0.000	0.986
$group_{25}$	0.530	0.349	0.000	0.981
$group_{26}$	0.460	0.349		0.972

$group_{11}$ represents $group_1$ visit1 at week1; $group_{12}$ represents $group_1$ visit2 at week3; and like $group_{26}$ represents $group_2$ visit 6 at week 11 respectively.

the efficacy of antiangiogenic therapies.[22,24-27] The low-dose chemotherapy drugs, as one-tenth of the MTD, administered continuously and frequently, could selectively suppress vessel growth in tumor tissues and prevent the repair of damaged vascular endothelial cells (VECs).[18] It is expected that this above-mentioned methods will be useful for OBD detection in MC trials. The application of time-dependent AUC was adopted through consideration of censored survival data[1]. In this work the AUC is presented as a function of time to detect the OBD. The estimates of AUC obtained through MCMC iterations. The AUC with time function is estimated through survival function. Recently, the Bayesian counterpart as a choice computation approach is also selected and found feasible and suitable.[28] The comparison of ROC curve estimators for a time-dependent outcome with marker-dependent censoring has also been attempted.[29,30] The marker specific threshold value has been obtained based on a performance of AUC. In this aspect another definition of sensitivity and specificity coined to discriminate the patients performance with failure up to time τ. The goal of this work is to present an approach to discriminate the patients according to their chance of appearance of recurrence based on threshold value of SM at time point τ on i^{th} individual. The corresponding ROC curve at time τ, called $ROC_i(\tau)$ obtained through relation plot of sensitivity and specificity in different threshold value i.e. $c_{i\tau}$.

The accuracy of the SM to predict the presence/absence of the failure *i* is measured by the area under the $ROC_i(\tau)$ curve. The performance of $AUC_i(\tau)$ obtained through posterior estimates. The posterior estimated generated through 20,000 iterations with 5,000 burns in refreshment. The 95% credible interval of AUC obtained are given in Table 2. The threshold value of SM will provide us opportunity to predict the individual's chances of appearance of recurrence during long-term follow-up and to detect the corresponding true value of AUC.

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